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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/827,498	04/19/2004	Liangjing Chen	6560US	3464

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EXAMINER	
HUTSON, RICHARD G	
ART UNIT	PAPER NUMBER
1652	
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06/20/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/827,498	CHEN ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-9,11-28,84-98,102-112,115-125 and 127-129* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *129* is/are allowed.

6)☒ Claim(s) *1,5-9,11-28,84-98,102-112,115-125,127 and 128* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's cancellation of claims 2-4, 10, 29-83, 99-101, 113-114 and 126 and the amendment of claims 1, 97, 98, 102, 103, 115, 127 and 129, in the papers filed on 2/15/2008 and 4/4/2008, is acknowledged. Claims 1, 5-9, 11-28, 84-98, 102-112, 115-125 and 127-129 are still at issue and are present for examination.

Applicants' arguments filed on 2/15/2008 and 4/4/2008, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 remain indefinite in that it recites a hyperactive reverse transcriptase comprising or corresponding to H638 or F155, without an amino acid sequence for reference. As was previously pointed out to applicants, "H638" and "F155" are relative terms and their recitation in the claims is unclear and indefinite without the amino acid sequence to which they are relative.

In response to this rejection, applicants have amended claim 1 to recite “with reference to wild-type M-MLV" and applicants traverse the rejection as it applies to the newly amended claims.

Applicants submit that one of skill in the art realizes that the N-terminal methionine residue may or may not be present in a protein sequence; similarly, leader sequences may or may not be present thereby affecting the numbering of each amino acid in a protein sequence. Applicants submit that one of ordinary skill in the art would readily recognize the mutation locations H638 and F155 by reference to a wild type sequence, as the specification teaches such a wild-type sequence in citing Accession No. J02255 in working Example 3; see the specification at page 23, lines 2-3. Applicant submits that amended independent Claims 1, 97, 98, 102, 115, mid I27 thereby are not indefinite.

Applicant’s amendment and complete argument is acknowledged and has been carefully considered, however, is not found persuasive for the reasons previously made of record and those repeated herein. When referring to an amino acid position, applicant’s reference to wild-type M-MLV remains indefinite because “wild-type M-MLV” does refer to a definitive amino acid sequence. Thus the claims remain indefinite in there reference to an amino acid corresponding to H638 and F155 with reference to wild-type M-MLV. Further, not only are the claims indefinite in the reference to position H638 or F155 of the wild-type M-MLV, but applicants recitation of a mutation “corresponding to” H638 or F155, further adds ambiguity to the claimed reverse transcriptase proteins. What does it mean to "correspond to" these referred to

positions? Thus claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 remain indefinite.

Claims 1, 5-9, 11-28, 84-97 are indefinite in that they recite "a mutation in the processivity domain corresponding to H638". It is unclear as to what is a mutation corresponding to H638. While previously the claims were drawn to a point mutation corresponding to H638, and this was interpreted as a point mutation corresponding to position H638, applicant's newly amended claims are unclear? Appropriate clarification or amendment is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection was stated in the previous office action as it applied to previous claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-129. In response to this rejection applicants cancelled claims 2-4, 10, 29-83, 99-101, 113-114 and 126 and amended claims 1, 97, 98, 102, 103, 115, 127 and 129 and traverse the rejection as it applies to the newly amended claims.

Applicants submit that the amino acid sequence of Moloney Murine Leukemia Virus reverse transcriptase protein is known and the reverse transcriptase gene may be obtained from pubic sources, or may even be purified from eukaryotic cells infected with a retrovirus or from a plasmid that includes a portion of the retrovirus genome that includes the RT. Applicants submit that the present specification also cites the Accession No. for the wild type M-MLV RT sequence as J09255 (working Example 3 at page 93, lines 9-3) and U.S. Patent 6,136,582 describes a reverse transcriptase of M-MLV having a substitution of valine at position I55. Applicants submit that therefore, the structures of the reverse transcriptase of M-MLV and at least one mutant thereof are known to one of ordinary skill in the art.

Applicants submit that the present specification has defined the processivity domain as generally corresponding to amino acids 497 to 671 of M-MLV reverse transcriptase and as can be seen by one of ordinary skill in the art, replacement of histidine with glycine effectively removes the side chain imidazole ring at position 638. Since there are 20 naturally occurring amino acids, a mutation of the histidine corresponding to position 638 can yield, at most, one of 19 other amino acids al that position. Applicants submit that a mutation at position F155 is known in the art (U.S. Patent 6,136,582 cited by the Office Action). Therefore, the number of members of the genus containing F155 and H638 mutation combinations is 19 X I9 or 361 combinations. Applicants submit that each combination can be written out using the wild type sequence of M-MLV and replacing the histidine-638 with one of each of 19 amino acids and replacing the phenylalanine-155 with one of each of 19 amino acids.

Applicants therefore submit that the invention as set forth by Claim 1 is fully described by the specification in light of knowledge of one of ordinary skill in the art.

Applicants submit that independent Claims 97, 98, I02, 115, and 127 recite a hyperactive reverse transcriptase protein comprising H638G with reference to wildtype M-MLV. Said independent claims therefore set forth one member of the genus of mutations at the histidine-638 position; specifically, the mutation in which position 638 is a glycine.

Applicants submit that for these reasons the invention as set forth by independent Claims 1, 97, 98, 102, 115 and 127 is adequately described in the specification.

Applicants amendment of the claims and applicants complete argument are acknowledged and have been carefully considered, however, these remain nonpersuasive for the reasons previously made of record and repeated herein.

It continues that applicant's claims are so broad as to be drawn to any mutant Moloney Murine Leukemia Virus reverse transcriptase protein comprising a mutation corresponding to H638 and a mutation corresponding to F155.

Applicant's arguments continue to address the rejection on the basis that the amino acid sequence of Moloney Murine Leukemia Virus reverse transcriptase protein is known and the reverse transcriptase gene may be obtained from pubic sources and a reverse transcriptase of M-MLV having a substitution of valine at position I55. Applicants submit that therefore, the structures of the reverse transcriptase of M-MLV

and at least one mutant thereof are known to one of ordinary skill in the art and that given this applicants submit that each combination can be written out using the wild type sequence of M-MLV and replacing the histidine-638 with one of each of 19 amino acids and replacing the phenylalanine-155 with one of each of 19 amino acids.

Applicants argument is considered flawed on the basis that without any structural limitation associated with the claimed mutant hyperactive reverse transcriptases beyond "a mutation corresponding to H638 or F155", the claimed genus of mutant reverse transcriptases is extremely broad and applicants description as well as that which was known in the art is insufficient to adequately describe the claimed genus of mutant reverse transcriptases.

Applicants arguments for independent Claims 97, 98, I02, 115, and 127 is similarly flawed based upon the same logic, that applicants claimed genus of mutant reverse trancriptases has no little to no structural limitations and is thus excessively broad.

It continues that the specification fails to describe additional representative species of these mutant reverse transcriptases by any identifying structural characteristics or properties other than the activities recited in claim 1, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-128 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the M-MLV reverse transcriptase comprising the amino acid sequence of SEQ ID NO: 2 consisting a mutation at position H638 and F155, does not reasonably provide enablement for any hyperactive M-MLV reverse transcriptase protein comprising a mutation in the processivity domain corresponding to H638 and a mutation in the nucleotide selection domain corresponding to F155. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The rejection was stated in the previous office action as it applied to previous claims 1, 5-9, 11-28, 84-98, 102-112,115-125 and 127-129. In response to this rejection applicants cancelled claims 2-4, 10, 29-83, 99-101, 113-114 and 126 and amended claims 1, 97, 98, 102, 103, 115, 127 and 129 and traverse the rejection as it applies to the newly amended claims.

Applicants submit that Claim 1 is to, in part, a hyperactive Moloney Murine Leukemia Virus reverse transcriptase protein having a mutation at Hislidine-638 with reference to wild type M-MLV.

Applicants have described how to construct mutants using mutagenic primers, how to express and purify mutant reverse transcriptases, how to measure RNase H activity of mutant reverse transcriptases, how to analyze cDNA products thereof and how to use the mutant reverse transcriptases in RNA amplification. Therefore, the tools and methods are provided for constructing a mutation at position H638 or" reverse transcriptase with reference to the wild-type M-MLV and the quantity of further experimentation for constructing such a mutant protein is not undue.

Applicants submit that the nature of the invention is that of reverse transcriptase structure and function, a relatively mature technology in that the tools are available for study and much is known about the structure and function of wild-type enzymes.

Applicants submit that it is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a genetic invention.

Applicants submit that one of Skill in the art is taught by the specification how to make and use the invention as set forth by the claims since, while certain experimentation would need to be carried out, such experimentation is not undue and is well within the skill of one in the art.

Applicants submit that in light of these teachings, including the working examples, one of ordinary skill in the art could readily construct each of the 361 mutant reverse transcriptases that have a mutation at H638 and a mutation at F155 as set forth

by independent Claim 1 and similarly, in light of these teachings, including the working examples, one of ordinary skill in the art could readily construct each of 19 mutant reverse transcriptases that have a mutation at H638 with reference to wild-type M-MLV as set forth by independent Claims 97, 98, 102, 115. 127, and 129.

As above under the response to the written description rejection applicant's amendment of the claims and applicants complete argument are acknowledged and have been carefully considered, however, these remain nonpersuasive for the reasons previously made of record and repeated herein.

It continues that applicant's claims are so broad as to be drawn to any mutant Moloney Murine Leukemia Virus reverse transcriptase protein comprising a mutation corresponding to H638 and a mutation corresponding to F155.

As in applicants response to the written description rejection applicants arguments continue to address the rejection on the basis that the amino acid sequence of Moloney Murine Leukemia Virus reverse transcriptase protein is known and the reverse transcriptase gene may be obtained from pubic sources and a reverse transcriptase of M-MLV having a substitution of valine at position I55. Applicants submit that therefore, the structures of the reverse transcriptase of M-MLV and at least one mutant thereof are known to one of ordinary skill in the art and that given this applicants submit that each combination can be written out using the wild type sequence of M-MLV and replacing the histidine-638 with one of each of 19 amino acids and replacing the phenylalanine-155 with one of each of 19 amino acids.

As above applicants argument is considered flawed on the basis that without any structural limitation associated with the claimed mutant hyperactive reverse transcriptases beyond "a mutation corresponding to H638 or F155", the claimed genus of mutant reverse transcriptases is extremely broad and applicants description as well as that which was known in the art is insufficient to enable the breadth of the claimed genus of mutant reverse transcriptases.

The specification continues to not support the broad scope of the claims which encompass all modifications and fragments of any the mutant M-MLV reverse transcriptase comprising a mutation in the processivity domain and a mutation in the nucleotide selection domain, corresponding to H638 and F155, respectively, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting the hyperactivity; (B) the general tolerance of M-MLV reverse transcriptases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a reverse transcriptase with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the reverse transcriptase activity claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable, it would require undue experimentation for one skilled in the art

to arrive at the majority of those polypeptides of the claimed genus having the claimed reverse transcriptase activity.

Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any modification and fragment of any mutant M-MLV reverse transcriptase comprising a mutation in the processivity domain and a mutation in the nucleotide selection domain, corresponding to H638 and F155, respectively. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those mutant reverse transcriptases having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

The rejection of claim 129 under 35 U.S.C. 102(b) as being anticipated by Gao et al. (U.S. Patent No. 6,136,582) is hereby withdrawn based upon applicants amendment requiring that the claimed reverse transcriptase comprise the amino acid sequence of SEQ ID NO: 2.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
6/17/2008

/Richard G Hutson, Ph.D./
Primary Examiner, Art Unit 1652